Unhealthy Bone

Introduction

This lesson is about the acquired disorders of bone—rickets/osteomalacia, osteoporosis, Paget's disease of bone—with a focus on what happens to the bone, as seen from bone's perspective. Bone embryology is not necessary for this to make sense, but having that knowledge makes this lesson easier. (Embryogenesis content has been made available as a supplement so as to limit the bulk of the main lessons.) To set the context for each disease and continue the discussion of embryonic bone growth, we start with a discussion of growth plates and bone growth. We follow with the diseases and close with the pharmacologic treatment of osteoporosis.

Growth of Long Bone After Birth

We start this next discussion when ossification is already complete. A growth plate (aka epiphyseal plate, aka metaphyseal plate) made of cartilage separates the bone and bone marrow of the epiphysis and metaphysis, whereas the bone and bone marrow of the diaphysis is continuous with those of the metaphysis. From here, there is no cartilage template to ossify, only a cartilage growth plate that makes long bones grow longer.

As bones grow longer, both external and internal remodeling must occur in order for them to retain their proportions and unique shape. Long bones grow longer because the growth plate **cartilage proliferates and is resorbed**, expanding the length of the marrow cavity and providing cartilage spicules as scaffolding for woven bone spicules to be built. The chondrocytes in the middle of the epiphyseal plate are the **zone of reserved cartilage.** From within that zone, chondroblasts proliferate. The growth plate height doesn't change because the proliferation from within the growth plate is matched by resorption and laying down of bone from without. But let's consider what happens, theoretically isolating growth and resorption from one another, as shown in Figure 4.1.

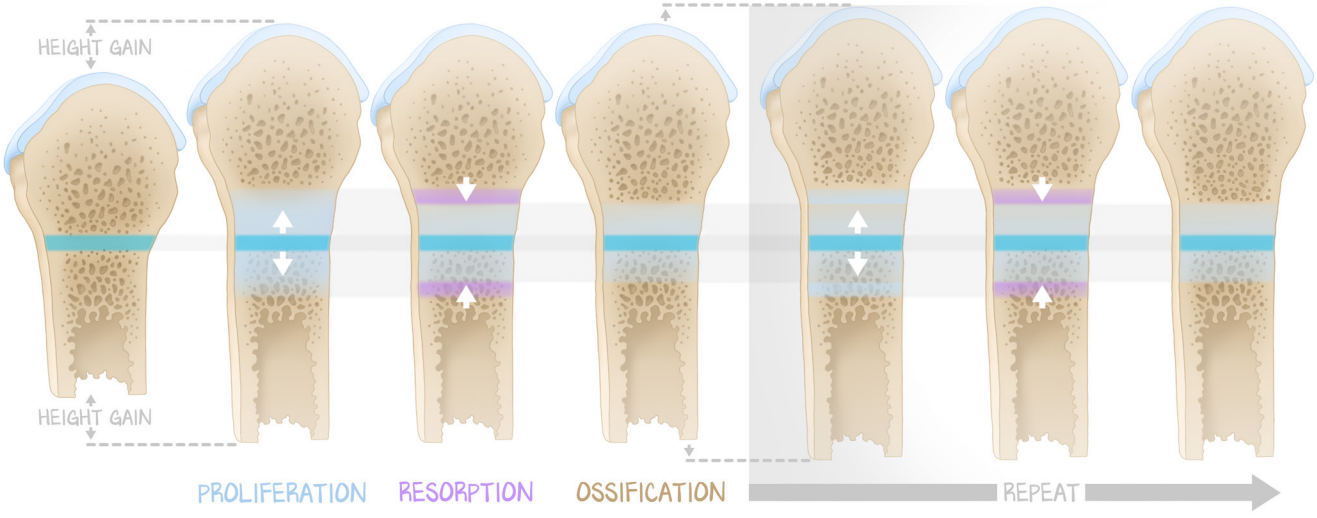

Figure 4.1: Bone Growth

The metaphysis side of the epiphyseal (growth) plate represents the primary ossification center. The epiphysis side of the growth plate represents the secondary ossification center. Chondrocytes replicate, elongating the bone by growing out towards the ossification centers. They then calcify and die, allowing resorption into the ossification center. Their calcification and death allow for osteoid deposition and the ossification of new bone.

Now to the other zones. Use Figure 4.2 to follow the text. The chondroblasts proliferate in the **zone of proliferation**. This would increase the size of the cartilaginous layer and growth plate. Trabecular bone would be pushed farther away from the growth plate. The bone gets longer in both directions. Preparing for more endochondral ossification, those chondroblasts farthest away from the center of the growth plate, farthest away from the proliferation, the oldest cells that are still cartilage, are in the **zone of hypertrophy** and undergo hypertrophy (they get bigger). They calcify their matrix, and because chondrocytes do not have canaliculi, that calcification restricts the diffusion of nutrients, so they die. This provides a different kind of cartilaginous template than in the development of the ossification centers but works the same way. Osteoblasts will use that cartilage and turn it into bone within the **zone of calcified cartilage**. From the zone of resorption, from the bone marrow, come blood vessels and osteoblasts to transform the calcified cartilage into bone. Within the **zone of resorption**, the calcified matrix is resorbed by osteoclasts, making room for more marrow.

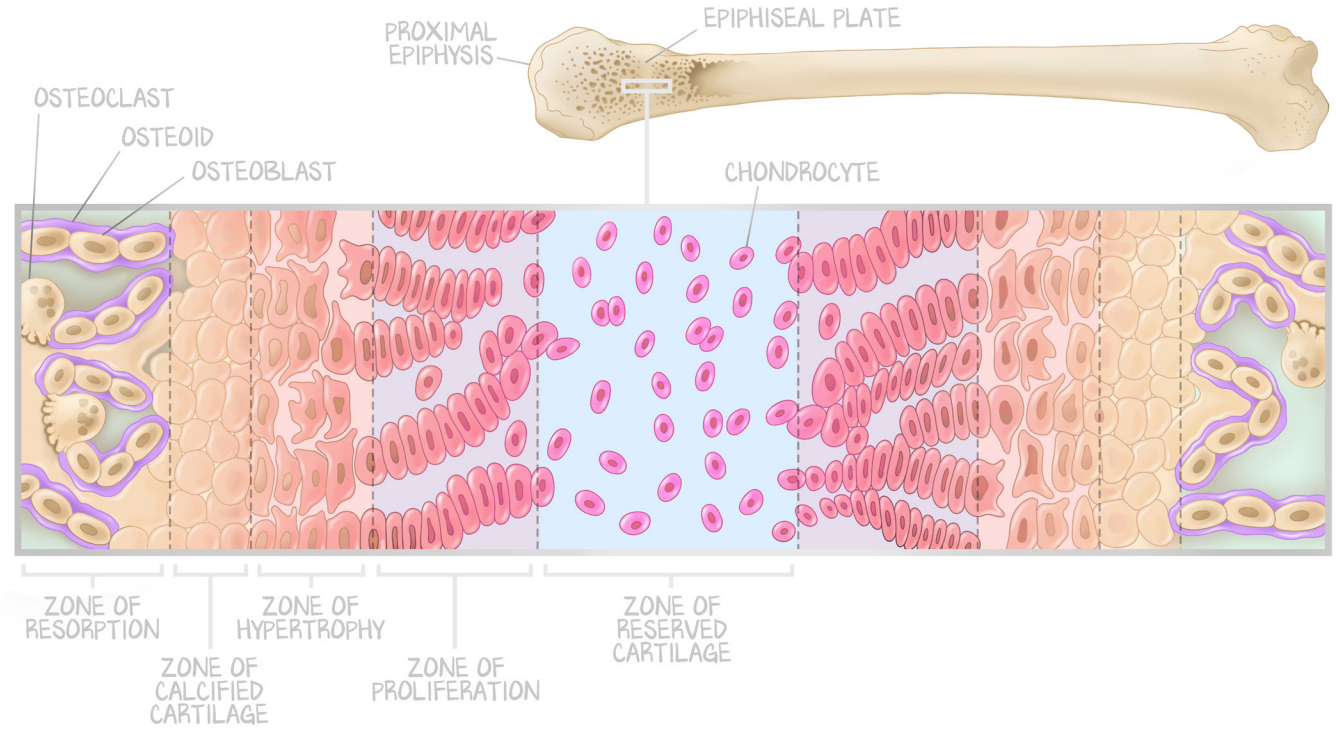

Figure 4.2: Histological Zones of Long Bone Growth
A visualization of the zones from the previous paragraph.

Acquired Bone Disease

Osteomalacia and **rickets** are the same disease with the same underlying cause. Osteomalacia is the phenotypic outcome if the pathogenesis occurs in adults, after fusion of the growth plates; rickets is the phenotypic outcome of the pathogenesis in children, before fusion of the growth plates. Both are caused by **vitamin D deficiency**. Vitamin D is a fat-soluble vitamin that can be ingested in the diet or synthesized by the skin with UV radiation exposure. Vitamin D's ultimate purpose is to be converted into active 1,25-vitamin D, which acts to increase phosphate and calcium absorption in the gut by promoting transcription of the Na/P_i and Na/Ca transporters (Parathyroid #1: *The Healthy Parathyroid*). 1,25-Vitamin D also stimulates osteoblasts to synthesize and secrete **osteocalcin**, which is required to mineralize osteoid (Parathyroid #3: *The Healthy Bone*). In vitamin D deficiency, there is less calcium absorbed from the gut and less osteocalcin to trap calcium in osteoid. This has two consequences.

First, **relative hypocalcemia** (as a result of vitamin D deficiency) is corrected by **increasing PTH**. The calcium is kept normal, but the PTH level is high, as in secondary hyperparathyroidism. Increased PTH stimulates osteoblasts to release RANK-L and suppress the expression of osteoprotegerin (OPG). This increases osteoclast activity that causes bone resorption, resulting in weakened, thin bones. More PTH means more resorption of bone. Because these conditions are caused by a nutritional deficiency, and therefore the patients have intact kidneys, the increased PTH also means the excretion of phosphate. This is a phosphate double whammy—insufficient phosphate from the diet and phosphate wasting in the kidneys due to the elevated PTH.

Second, less osteocalcin means less mineralization of osteoid. New bone formation, whether during embryonic development or remodeling, produces osteoid that has difficulty ossifying. Endochondral bone growth is also affected by inadequately calcifying the cartilage template, resulting in the persistence of chondrocytes. The persistence of cartilage means the osteoid of woven bone is released into an inadequately mineralized medium. The lack of mineralization does two things. First, without the mineralization of osteoid, there will be a **radiolucency of all cortical bone**, caused by the failure of mineralization of osteoid created in the process of remodeling. Second, without mineralization of osteoid and persistence of chondrocytes, radiographically, the **space occupied by the growth plate appears larger**. Chondrocytes don't calcify their matrix. Osteocytes don't ossify their osteoid. Chondroblasts in the zone of proliferation continue to proliferate. The epiphyseal cortex is pushed farther from the diaphyseal cortex, so the bond gets longer, but the radiopaque mineralized bone cannot be seen. This presents as the growth plate widening on X-ray.

The gross skeletal changes in rickets depend on the severity and duration of the process and, in particular, on the stresses to which individual bones are subjected. During the **nonambulatory** stage of infancy, the head and chest sustain the greatest stresses. The softened occipital bones may flatten. The parietal bones are weak, so when an examiner applies pressure, they buckle inward, a process called **craniotabes**. With the release of the examiner's pressure, elastic recoil snaps the bones back into their original positions. An excess of osteoid in the **frontal bone** produces **frontal bossing** and a squared appearance to the head. Overgrowth of costal cartilage or osteoid tissue at the costochondral junction produces the "**rachitic rosary**." The normal rigid ribs that resist the diaphragm's pull that enables inspiration are weakened, succumb to the pull of the diaphragm, and thus bend inward, creating anterior protrusion of the sternum, called **pigeon breast deformity**. When **ambulatory**, with stress applied to the axial skeleton and legs, a child will develop spine, pelvis, and tibia problems. This results in **lumbar lordosis** and **bowing of the legs**.

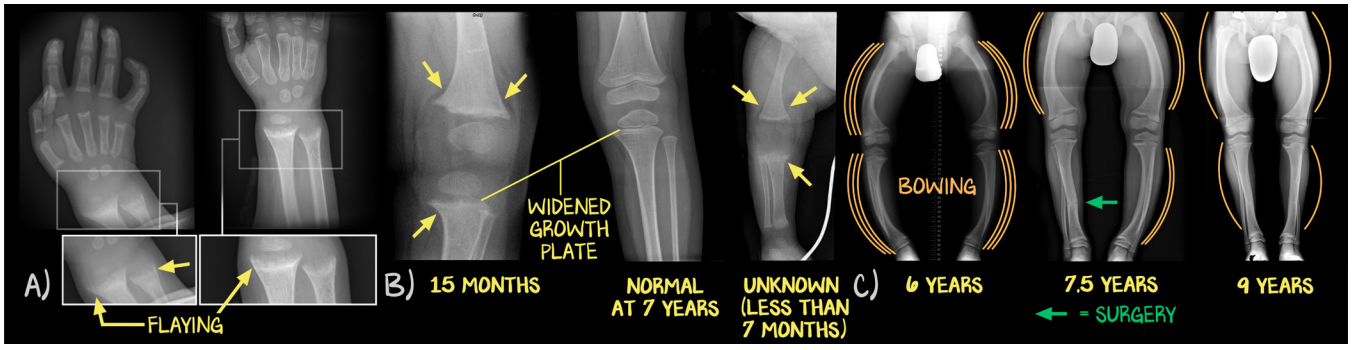

Figure 4.3: Radiographic Rickets
(a) The hand of a normal child (lower) is used to compare to the wrists and hands of children with rickets. These bones do not bear weight, so they do not bow, but you can see flaring of the radius and a widened growth plate (radial epiphysis is far from the radial metaphysis). (b) The same thing, only in the leg. The femurs show flaring; the tibia on the left shows flaring and widened growth plate (more space between the epiphysis and metaphysis. (c) X-ray series of a child with bowed legs due to rickets. At 6 years old, the bowing is severe; however, notice the lack of flaring and the normal growth plate space. This child no longer has rickets, but the bowing remains. At year 7, the child underwent surgery to correct the right tibia (left side of image). At year 9, the femur deformities persist, but the tibial deformities improved.

In adults with vitamin D deficiency who develop **osteomalacia**, the developmental issues are not present. Thus, there are **no skeletal deformities.** However, the lack of vitamin D deranges normal bone remodeling. Osteoclasts clear good bone. Osteoblasts form the new osteon. But whoops, newly formed osteoid matrix laid down by osteoblasts in the BMU (Parathyroid #3: *The Healthy Bone*) is inadequately mineralized. Inadequately mineralized osteoid results in excess osteoid found on biopsy of a bone in a patient with osteomalacia. Inadequately mineralized osteoid results in weakened bone. Although the contours of the bone are not affected (no skeletal deformities), the **bone is weak** and **vulnerable to fractures**. The unmineralized osteoid will give the cortical bone a more **translucent appearance** on X-ray.

Osteomalacia is not simply weakened bone (that would be osteopenia and osteoporosis). Osteomalacia has very active bone, stimulated by PTH. Osteoblasts are trying to build bone, to mineralize their osteoid. Part of the mineralization process is the liberation of phosphates from extracellular matrix proteins by the actions of **alkaline phosphatase** (ALP). In osteomalacia, ALP is elevated. In osteomalacia, **25-vitamin D is reduced** (diagnosis of vitamin D deficiency is with the more stable precursor to active vitamin D, because active vitamin D can change with PTH levels), **calcium is normal** or decreased, and **phosphate is decreased**. The enhanced remodeling of bone stimulated by PTH results in **bone pain**.

Vitamin D is a **fat-soluble vitamin** made by the skin. Causes of vitamin D deficiency are **insufficient sun exposure** (in someone who also does not get sufficient vitamin D from their diet), **fat malabsorption** (as seen in terminal ileum inflammation of Crohn's disease), and **malnutrition** (as is most commonly seen in impoverished or developing countries). Treatment is to **give vitamin D** to avoid the problems of mineralizing cartilage and osteoid and **give calcium** to turn off the PTH-induced resorption of bone.

Osteoporosis

Osteopenia and **osteoporosis** represent histologically normal bone that is decreased in quantity, but osteoporosis is sufficiently severe to increase the risk of fracture significantly. They are the **same diagnosis, the same disease**, except we call it osteoporosis when the severity of osteopenia reaches a certain threshold. The disease is very common with marked morbidity and mortality from fractures. Multiple factors, including peak bone mass, age, activity, genetics, nutrition, and hormonal influences, contribute to its pathogenesis.

Osteoporosis is about two things: how well a patient builds **peak bone mass** and how well a patient **staves off bone loss**. Until around age 30, bone density increases. When the peak bone mass is reached, there is a progressive loss of bone every year. Behaviors and genetics during the building period determine what the peak will be. Behaviors and sex (both more so than genetics) determine how precipitous a decrease in bone mass there will be. Because the underlying process is an outpacing of bone-clearing (osteoclast activity) over bone-building (osteoblasts), the bone regions most affected will be ones with the greatest surface area exposed to osteoclasts—regions of **trabecular bone**. Trabecular bone is found in the vertebrae and at the ends of long bones.

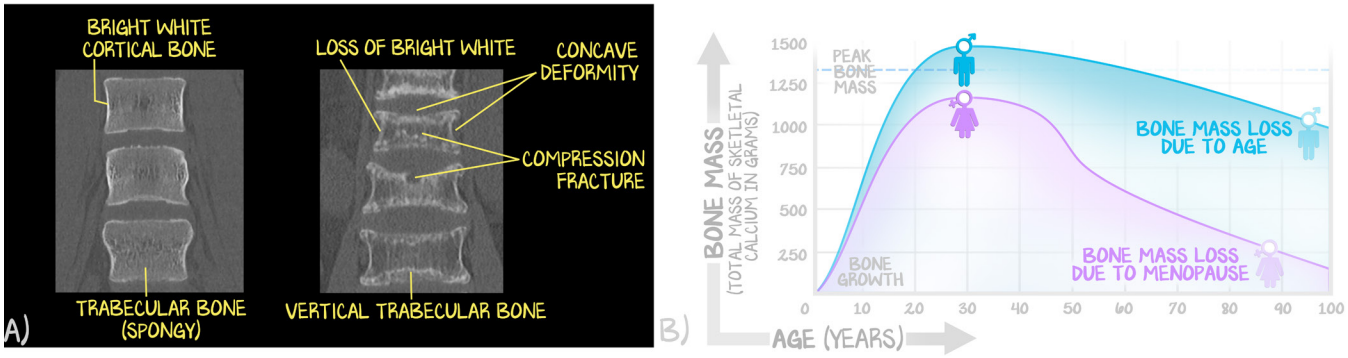

Figure 4.4: Osteoporosis
(a) Bone window CT of a patient with normal vertebrae (left) and a patient with osteoporosis (right). Loss of lucency of the cortical bone, vertical trabecular markings (instead of every which way), compression fractures, and concavity of the cortical bone are seen. There is also a loss of overall volume. (b) Women are at higher risk than men for osteopenia and osteoporosis due to a lower peak bone mass and a more precipitous drop in bone mass due to menopause.

Physical activity affects both peak bone mass and the rate of bone loss. Because muscle contraction is the dominant source of skeletal loading, resistance exercises, such as weight training, are more effective stimuli for increasing bone mass than repetitive endurance activities, such as bicycling. The decreased physical activity that is associated with normal aging contributes to senile osteoporosis.

Calcium nutrition affects both peak bone mass and the rate of bone loss. Any stimulation of endogenous PTH is going to accelerate the clearing of bone. Limiting remodeling to only what the bone needs to remodel (as opposed to extra remodeling to satisfy calcium needs) ensures minimal involvement from the parathyroid axis. **Vitamin D and Ca^{2+}** supplements are good for general health and are mandatory for postmenopausal women.

Estrogen status affects both peak bone mass and the rate of bone loss. Estrogen's mechanism in bone health has not been determined, but its impact has been. Women are at higher risk for developing osteoporosis because of the loss of estrogen that accompanies menopause. Empirical data have revealed that postmenopausal women have the most precipitous decline in bone density. Estrogen replacement does improve bone density, but the risks of endometrial and breast cancers make it unacceptable in most patients. SERMs (as discussed in the Reproduction module on breast cancer treatments) are sometimes used instead.

Unlike in osteomalacia, which is driven by an overactive PTH system, in osteoporosis, **calcium, phosphate, PTH,** and **ALP levels are normal**. Thus, there are no symptoms of osteoporosis until a fracture happens. This implies two things. First, **asymptomatic screening** is required for populations at risk. Second, anything that does increase the activity of PTH will exacerbate the development of osteoporosis. Therefore, the mainstay of therapy is to **exercise** and **give vitamin D and Ca^{2+}**. These are not treatment measures but preventative measures. Because the highest risk is in postmenopausal women, all postmenopausal women should be put on calcium and vitamin D supplementation. Avoiding the things we know empirically to cause osteoporosis is also key—**avoid smoking**, **alcohol**, and **glucocorticoids**.

The clinical manifestations of osteoporosis depend on which bones are involved. Vertebral fractures that frequently occur in the thoracic and lumbar regions are painful, and, when multiple, can cause significant loss of height and various deformities, including lumbar lordosis and kyphoscoliosis. **Pathologic fractures** may bring undiagnosed osteoporosis to light, especially in elderly white women who have a fall from standing. Diagnosis via **asymptomatic screening** with a DEXA scan is preferred to making the diagnosis after a fracture. X-rays are not good screening tools. DEXA scans are. At this point in your training, all you need is, "DEXA scans screen osteoporosis."

Osteoporosis Pharmacology

If someone is found to be osteopenic on screening, several treatment options are available.

The mainstay of osteoporosis treatment is with **bisphosphonates**. Bisphosphonates work by binding to ossified bone, specifically the phosphonate to calcium. When osteoclasts clear bone, they end up taking the bisphosphonates into their cytoplasm. This results in **osteoclast inhibition** and **apoptosis**. Because the only way bone density decreases is by osteoclasts clearing bone, inhibition and limitation of osteoclasts seem to make sense. The **oral** agents (alendronate, risedronate) cause **esophagitis** and **esophageal ulcers**, a product of the bisphosphonate molecule on the gastric mucosa. Because the mechanism is for the bisphosphonate to get tangled up in bone, steady-state levels are not necessary. Thus, oral agents are taken **weekly**. Other bisphosphonates (zoledronate, pamidronate) are **intravenous** and can be given as infrequently as **once a year**. The infrequent dosing is convenient, and the intravenous application avoids the esophageal symptoms. **Osteonecrosis of the jaw** is the major side effect of all bisphosphonates but has a higher incidence in the intravenous drugs.

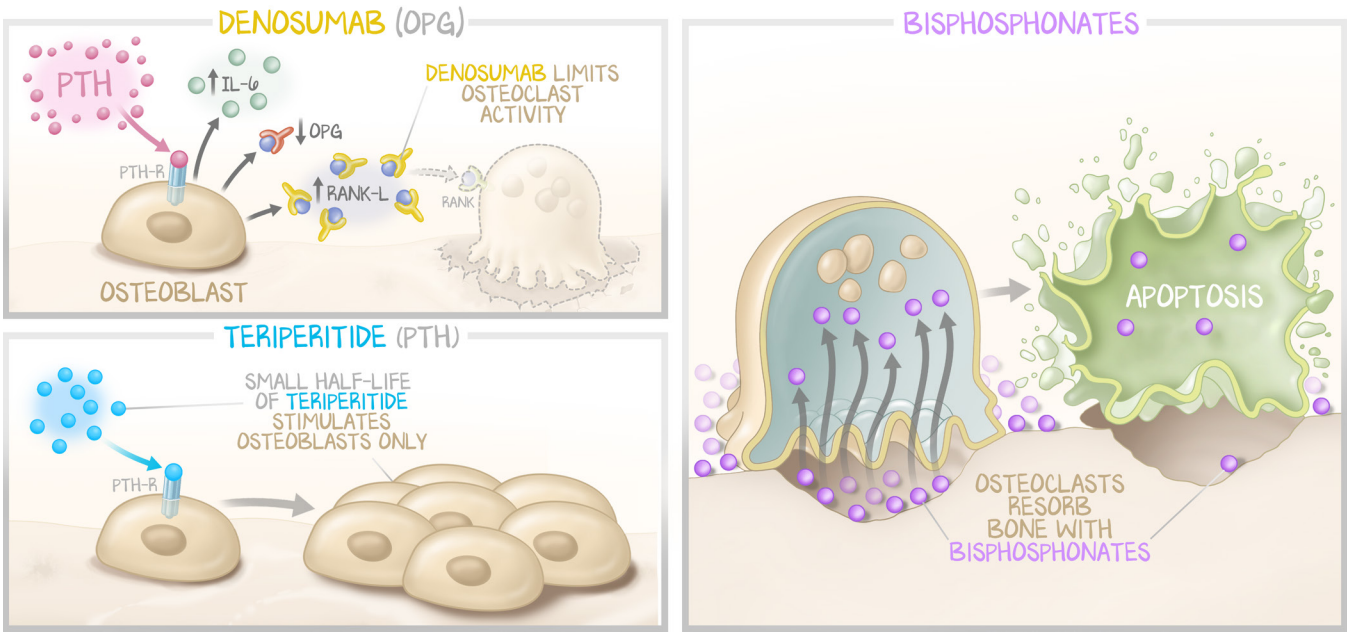

Figure 4.5: Osteoporosis Pharmacology
A visual representation of the mechanisms of action using illustrations that you are already familiar with. Denosumab is OPG. Teriparatide is PTH, but with a shorter half-life and only the osteoblast proliferation effect is felt, not the osteoclast stimulatory effect. Bisphosphonates poison osteoclasts when they resorb bone with bisphosphonate on it.

Denosumab is a recent development in the treatment of osteoporosis. It is a human **monoclonal antibody** that acts like OPG. It serves as a RANK-L decoy receptor, limiting the effect of PTH on osteoclast activity. Denosumab is given **twice a year** and is the preferred agent in patients who cannot tolerate bisphosphonates. Incredibly coincidentally, because the two medications use completely unrelated mechanisms, denosumab is characterized exactly the same as bisphosphonates: "osteonecrosis of the jaw, along with infrequent dosing."

All the interventions discussed so far—bisphosphonates, calcium, vitamin D, denosumab—have focused on limiting osteoclast activity. Only one treatment focuses on the active stimulation of osteoblasts. **Teriparatide** is a PTH analog. When given in short bursts, PTH actually stimulates osteoblasts. It must not be used in a patient with a proliferative bone disorder, such as cancer or Paget's disease. It is given

twice daily, subcutaneously, for up to two years. It is best used in **glucocorticoid-induced osteoporosis**, especially in patients in which steroids cannot be stopped. It can also be used short-term following thyroid- or parathyroidectomy while the parathyroids get revved back up.

Finally, there are secondary causes of accelerated osteoporosis. Hyperthyroidism (or too much levothyroxine), hypercortisolism (or too many glucocorticoids), and hyperparathyroidism (too much PTH) all drive increased bone turnover.

Paget's Disease of Bone

Paget's (rhymes with gadgets; James Paget was English, not French) disease of bone is a disorder of locally **increased** but also **disordered bone** in the **elderly**. Typically asymptomatic, it is usually discovered incidentally. Occurring later in life, most patients with Paget's disease of bone are over the age of 70. It is the opposite of osteoporosis. In the later stages of the disease, the time at which you would make the diagnosis, there is **decreased osteoclast activity** and **ongoing osteoblast activity**. The pathogenesis has still not been elucidated. In all cases of Paget's disease of bone that have been studied genetically, numerous mutations have been found. The genetics are too variable to definitively say what the gene or mutation is. But in all cases, the result of those variable mutations is increased expression of NF-κB in osteoclasts. That means increased osteoclast differentiation and activity.

Osteoclasts clear bone. How could this disease be gain-of-function in osteoclasts, and yet be one of excess bone deposition? The same reason that osteoporosis is the inevitable outcome for most patients—cellular **senescence**. Without this mutation, there would be no increased proliferation of osteoclasts. With this mutation, the early phase of the disease would resemble osteoporosis, with increased activity of osteoclasts. But because there is accelerated replication and differentiation, the osteoclast cell line burns out. Osteoclasts are produced in less abundance. Osteoblasts in this condition maintain their normal function and number. After the accelerated osteoporosis phase, during which the osteoclast precursors run out of divisions, the osteoblasts win.

Said histologically, there are waves of osteoclast activity and numerous resorption spaces in the initial lytic phase. The osteoclasts are abnormally large and have much more than the normal 10–12 nuclei; sometimes 100 nuclei are present, indicating upregulated differentiation and activation. In the subsequent **mixed phase**, osteoclasts decrease in number. In the final **sclerotic phase**, osteoblasts are abundant and osteoclasts barely visible.

Osteoclasts are essentially for remodeling. They are needed by the BMU to carve out the future osteon. Without them, in the sclerotic phase, bone is made, but not remodeled. The bone that is made is not in osteon patterns. In the end, the bone is composed of coarsely thickened trabeculae and cortices that are soft and porous and lack structural stability. These aspects make the bone vulnerable to deformation under stress; consequently, it fractures easily. The hallmark is a **mosaic** pattern of lamellar bone, seen in the sclerotic phase. This jigsaw puzzle-like appearance is produced by **unusually prominent cement lines**, which join haphazardly oriented units of lamellar bone.

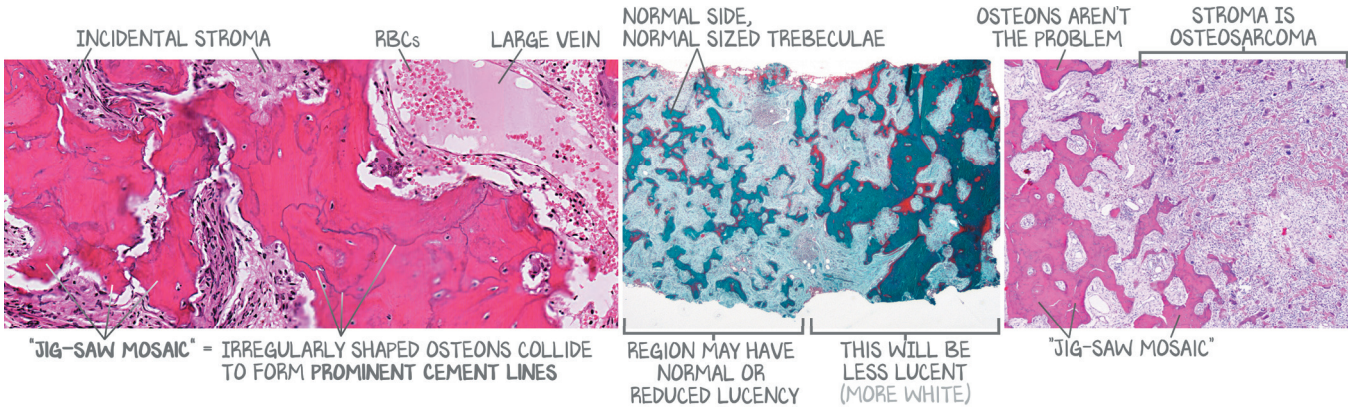

Figure 4.6: Histological Paget's Disease of Bone
Even the non-eponym osteitis obliterans is a misnomer, so we continue to use Paget's disease of bone. Paget's disease of bone starts with overactive osteoclasts resulting in bone resorption, leading to radiolucency similar to that seen in hyperparathyroidism. But when the osteoclast progenitors become senescent, the osteoblasts are left unchecked and without guidance (no resorption canal for the BMU), and so haphazardly lay down new osteoid. (a) This leads to thickened trabeculae (no bone clearing, only building) and the hallmark histology of a jigsaw mosaic with prominent cement lines. There is no resorption canal, so the borders of neighboring osteons abut one another (jigsaw-like means "not round"), and every osteon in contact with another is not cleared, causing two cement lines to become adjacent to one another (prominent). (b) Very low magnification showing sclerotic bone (more dark green) adjacent to atrophied bone (less dark green), a product of the antecedent osteoclast overactivity. (c) Paget's disease of bone makes large trabeculae (left) and predisposes to cancer (right). This magnification is so low that you cannot discern the cancer; there is merely a lot of bone (dark pink) on the left, and many cells (each purple speck is a cell, and each purple circle is a cluster of malignant cells).

The patient will complain of a gradual increase in the size of the bones. Similar to the story told in acromegaly, hat sizes will increase, and rings will stop fitting, although the change is gradual. The patient will be very old (over 70 years old). At the site of affected bones, there may be **bone pain**. And because osteoblasts are active, there is an **elevated ALP level**. The **X-ray** will reveal the changes—sclerotic (more white), enlarged (wider), and often deformed bone. Unfortunately, there isn't anything to be done about it. Short of a bone marrow transplant (to give more osteoclast precursors), there aren't any effective treatments that can bring a cell line back. And because this disease happens in old age, patients usually die with it, not from it, and would not likely survive a bone marrow transplant.

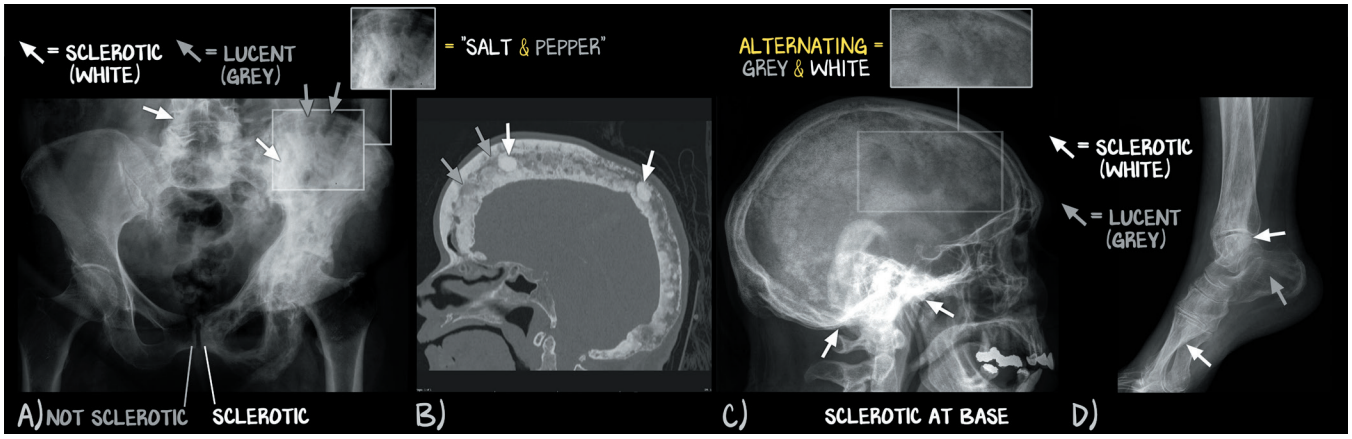

Figure 4.7: Radiographic Paget's Disease of Bone
The last figure identified histological sclerosis (after the osteoclast lineage is spent) and atrophic bone (a product of osteoclast overactivity). This leads to bone with lots of calcified matrix (sclerotic, more white than normal on films) neighboring other bone with very little calcified matrix (osteopenic, more grey than normal on films). (a) Pelvic film showing the "salt and pepper" pattern (alternating white and grey, indicating sclerosis and osteopenia, respectively) in the spine and pelvis, affecting the left side (right of the image). The right is relatively normal. (b) Sagittal CT showing increased skull size with alternating lucent and sclerotic regions. (c) The classic head x-ray showing sclerosis at the base and the "salt and pepper" pattern on the skull. (d) Another example of lucency (the talus) and sclerosis (metacarpal, talus, and calcaneus).